SPECIAL CONSIDERATIONS FOR INTEGRATED INFLUENZA VACCINE DEVELOPMENT IN LOW RESOURCE SETTINGS

8th WHO meeting on development of influenza vaccines that induce broadly protective and long-lasting immune responses

August 23-24, 2016
Chicago, IL
OBJECTIVES

- To discuss considerations for integrated development for next-generation influenza vaccines in low resource settings
  - Clinical
  - Clinical assays
  - CMC

- To address differences in development for low vs. high resource settings given that parallel development in both settings is the most likely scenario

- To provide suggestions for the path forward
CHALLENGES OF VACCINE DEVELOPMENT FOR LOW RESOURCE COUNTRIES

**Timing gaps between initial approvals and uptake in low income countries**

- PCV Approved 2000
- PCV WHO PQ 2010
- PCV 31% coverage (50% AFRO) 2015
- Rota Approved 2004-6
- Rota WHO PQ 2009
- Rota 19% coverage (30% AFRO) 2015

### Challenges that have led to gaps

- Inadequate supply
- Product profiles not optimal
  - Large cold-chain footprint
  - High costs
  - Inadequate strain-coverage
  - Immunity/efficacy lower than desired (lower than in high income countries)
- Clinical/manufacturing data necessary for WHO PQ not available with initial regulatory approval
- Lack of financial incentives and opportunity costs (most relevant for multinational companies)
WHAT IS INTEGRATED VACCINE DEVELOPMENT?

- **TPPs** set the direction for vaccine development

- **R&D Milestones** define expected outcomes

- **Integrated Product Dev. Plan (IPDP)**
  - Clinical
  - CMC
  - Regulatory
  - Timelines, Risks, Progress

- **Stage-gate Reviews**
  - Review of key data
  - Forward looking discussion on the next stage of development
Clinical Development Considerations for Next-Generation Influenza Vaccines
PREFERRED PRODUCT CHARACTERISTICS: DIFFERENCES FOR LOW VS. HIGH RESOURCE COUNTRIES

**Indication:** Prevention of severe laboratory-confirmed influenza illness caused by human influenza A infection

- Current indication for seasonal vaccines is for immunization against influenza disease, severity not specified

- Effectiveness against severe illness has been evaluated in HICs using healthcare-associated visits as a marker of severity. These outcomes may not be relevant for low resource settings.

- An objective method for defining severity independent of the healthcare system will be important
  - Ex: Scoring systems for rotavirus and RSV vaccines

- It will also be important to clarify the magnitude of desired efficacy as well as breadth and duration
Target Population: Persons 6 weeks and older belonging to a group at high risk for severe influenza illness

- High risk groups include children aged 6 weeks to 59 months, elderly persons, persons with chronic medical conditions, and pregnant women

- Clinical trials are complex in these vulnerable populations in low resource settings
  - How will these populations be identified?
  - Additional ethical considerations?

- Dosing is also important to consider – will the same dose/regimen be appropriate for all groups?

- If clinical trial data are favorable, are there delivery platforms to enable high coverage rates?
PREFERRED PRODUCT CHARACTERISTICS: DIFFERENCES FOR LOW VS. HIGH RESOURCE COUNTRIES (CONT)

**Target Population:** Consider also school-aged children, pregnant women, and health care workers

- Vaccine for efficacy against non-severe, laboratory confirmed influenza illness may be appropriate with substantial indirect effects
  - Protection in neonates/young infants
  - Prevent transmission to community

- Maternal vaccination has been shown to protect neonates/infants against influenza illness

- Are studies showing reduction in community transmission through vaccination of school-aged children feasible in low income countries?
  - Pre- vs. post-licensure
Clinical Assay Considerations for Next-Generation Influenza Vaccines
CLINICAL ASSAY CONSIDERATIONS FOR NEXT-GENERATION INFLUENZA VACCINES

• Current immunogenicity assays are likely insufficient to demonstrate improved magnitude, breadth, and duration of efficacy of next-generation vaccines

• Immunologic correlates of protection would simplify the development process of next-generation vaccines but are unlikely to be available for initial registration
  • Efficacy data will be needed to establish correlates
  • Correlates may differ across platforms

• Immunologic techniques are available/advancing to more fully characterize the immunologic profiles of next-generation vaccines
  • Is it feasible/needed to utilize these for low resource settings?

Questions

1. How will dose be determined in phase 2 studies before implementing large phase 3 efficacy trials?
2. Is it possible that dose/regimen should be different for different high risk groups?
CMC/Manufacturing Development Considerations for Next-Generation Influenza Vaccines
CMC/MANUFACTURING DEVELOPMENT

- Chemistry, Manufacturing, and Controls encompasses the development activities needed to physically make products
  - Bioprocess
  - Formulation
  - Analytics

- For vaccines, CMC development must be highly integrated with clinical development and programmatic/delivery needs
  - Bioprocess efficiency affects capacity and cost
  - Formulation affects immunogenicity, stability/shelf life, and ease of administration
  - Analytical assays characterize the consistency of the manufacturing process
    - Potency assay(s) is critical for properly identifying dosage
### POTENTIAL CMC TECHNOLOGY PLATFORMS FOR NEXT-GENERATION INFLUENZA VACCINES AND IMPLICATIONS FOR LOW RESOURCE COUNTRIES

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<th>Technology Platform</th>
<th>Challenge</th>
<th>Implications</th>
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<td>Live viral; inactivated vaccines</td>
<td>Yields; reactogenicity</td>
<td>• Capacity; high cost of manu</td>
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<td>• Additional safety data</td>
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<tr>
<td>Recombinant proteins</td>
<td>Magnitude and duration of immunogenicity/efficacy</td>
<td>Higher dose and/or adjuvants may be required</td>
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<td>Vector-based vaccines</td>
<td>• Vector immunity</td>
<td>• Potential impact on efficacy</td>
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<td>• Similar challenges as live virus vaccines - yields, reactogenicity</td>
<td>• Potential larger safety database</td>
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<td>• Capacity; high cost of manu</td>
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<tr>
<td>Nucleic acid vaccines (RNA/DNA)</td>
<td>• Delivery formulations and/or devices</td>
<td>• Higher dose may be required</td>
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<td>• Dose volume</td>
<td>• Longer development timeline</td>
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<td>• Higher delivery cost</td>
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<tr>
<td>Novel adjuvants</td>
<td>Mechanism that provides improved, longer duration efficacy with an</td>
<td>• Potential larger safety database</td>
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<td>acceptable safety profile</td>
<td>• Higher cost of manu</td>
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ALTHOUGH COMPLEX, IT WILL BE POSSIBLE TO DEVELOP NEXT-GENERATION INFLUENZA VACCINES FOR LOW RESOURCE SETTINGS

• Be clear about desired product characteristics. Begin with the end in mind. Be quantitative.

• Engage in dialogue with regulatory authorities and WHO early

• Early development
  ▪ Consider small studies to characterize immunologic profile
  ▪ Consider small studies to iterate on dose/regimen (similar to process utilized for drug development)
  ▪ Consider developing and validating a severity score
  ▪ Partner with delivery colleagues on how high risk patients will be identified in late development. Can phase 3 trials be used to demonstrate feasibility of delivery as well as efficacy?
  ▪ Use preclinical and early clinical data to guide level of risk-taking on CMC development (i.e., what is the right timing for bioprocess and formulation optimization?)

• Late development
  ▪ Consider obtaining an indication in the highest risk population first followed by additional studies post-licensure in other populations of interest
  ▪ Get guidance from delivery colleagues on the balance between acceptable vs. optimal cost and presentation
THE WORK IS COMPLICATED.
WHY WE DO IT IS NOT.